Ms. Esther Barajas-Ochoa
OEHHA
P.O. Box 4010, MS – 128
Sacramento, CA 95812-4010

May 18, 2017

RE: Glyphosate NSRL

Dear Ms. Barajas-Ochoa,

The State of California must be commended for its ground-breaking actions to protect its citizens from the risks posed by glyphosate. I am concerned that the proposed NSRL of 1100 micrograms per day does not reflect the fact that there is no threshold for endocrine disruptors such as glyphosate.

Endocrine disruption may occur at ultra-low non-toxic levels. Low and environmentally relevant concentrations of glyphosate possess estrogenio actitivity. The estrogenicactivity of glyphosate is mediated by estrogen receptors. "Glyphosate promotes breast cancer in human cells at very low concentrations of 10 -12 to 10 -16." (1) Because hormones work at very low doses, endocrine disruption can occur from low dose exposure to hormonally active chemicals such as glyphosate. (2) As endogenous estrogen is already above the threshold for estrogen-mediated responses, there can be no threshold for responses to exogenous chemicals that act as hormone mimics via estrogen receptor mechanisms. (3)

Disease risk due to endocrine disrupting chemicals (EDCs) may be greatly underestimated as humans are simultaneously exposed to many EDCs. (4) The WHO/UNEP State of the Science of endocrine disrupting chemicals, 2012, states:

> "Endocrine disruptors produce non-linear dose responses both in vitro and in vivo. These non-linear dose responses can be quite complex and often include non-monotonic dose responses. They can be due to a variety of mechanisms; because endogenous hormones fluctuate, no threshold can be assumed." (5)

Glyphosate Based Herbicides (GBHs) may affect estrogen-regulated genes in human cell lines. (6) Adjuvants enhance glyphosate toxicity, bioavailability, cell penetration and bioaccumulation. Glyphosate-mediated toxic effects characterizes it as a potential endocrine disruptor. (7)(8)(9) Chemical mixtures in formulations appear to be underestimated regarding their toxic or hormonal impact. (10) "....The failure to account for combined effects in particular with adjuvants will undoubtedly lead to the underestimation of potential hazards, especially at the endocrine disruption level..." (11)

Roundup and Glyphosate are endocrine disruptors and therefore non-linear dose-responses may apply for some endpoints. (12) Non-linear and sex-specific effects should be considered as potential indications of endocrine disruption. Effects of reproductive toxicity are not restricted to a single generation and must be studied in trans-generational studies. (13) It is

possible that children, pregnant women and other vulnerable populations may be more susceptible to glyphosate exposures. (14) Higher glyphosate levels during pregnancy are correlated with low birth weights and earlier births. The outcome may be even more severe for the following generation. (15)

A thorough assessment of GBH toxicity should consider impacts such as potential endocrine disruption and multi-generational effects. (16) Calculation of thresholds for exogenous endocrine disruptors should include persistence, bioaccumulation, mechanisms of action and synergistic effects with other xenobiotics. (17) "Substances with endocrine disrupting properties are targeted within the European Union Registration, Evaluation, Authorization, and Restriction of chemicals (REAR). Identification of substances as endocrine disruptors may lead to their inclusion on the list of Substances of Very High Concern (SVHC)". (18)

In conclusion, the absence of a threshold for endocrine disrupting chemicals, such as glyphosate, has been demonstrated. It is important to consider non-linear dose responses to estimate actual risk. Complex effects must consider: 1). Endocrine disruption, 2). Combined effects with adjuvants, 3). Multi-generational effects, and 4). Synergism with other xenobiotic chemicals. Failure to consider these may lead to the underestimation of potential hazards from glyphosate, especially to vulnerable populations.

Sincerely,

Nancy O'Mara

Nancy O'Mara, MPH
Dennis, Massachusetts

**Glyphosate NSRL**

(1) Glyphosate induces human breast cancer cell growth via estrogen receptors. 2013 Thongprakaisang et al.

(2) Genetically engineered crops, glyphosate and the deterioration of health in the U.S.A. 2014 Swanson et al.

(3) Large effects from small exposures: 1. Mechanisms for endocrine disrupting chemicals with estrogenic activity. 2003 Welshong et al.

(4) The impact of Endocrine Disruption: A consensus statement. 2013 Bergman et al.

(5) State of the Science of endrocine disrupting chemicals. 2012 United Nations Environment Programme and the World Health Organization.

(6) Glyphosate-based herbicides (GBHs) are toxic and endocrine disruptors in human cell lines. 2009 Gasnier et al.

(7) Differential effects of glyphosate and Roundup on human placental cells and aromatase. 2005 Richard et al.

(8) Ethoxylated adjuvants of GBHs are active principles of human cell toxicity. 2013 Mesnage et al.

(9) Glyphosate formulations induce apoptosis and nerosis in human umbilical, embryonic and placental cells. 2008 Benachour et al.

(10) Co-formulations in glyphosate-based herbicides: disrupt aromatase activity in human cells below toxic levels. 2016 Defarge et al.

(11) Time and does-dependent effects of Roundup in human embryonic and placental cells. 2007 Benachour et. Al.

(12) Teratogenic effects of glyphosate-based herbicides: divergence of regulatory decisions from scientific evidence. 2012 Antonion et al.

(13) Potential Toxic effects of glyphosate and its commercial formulations below regulatory limits. 2015 Mesnage et. al.

(14) Endocrine disruption and cytotoxicity of glyphosate with Roundup in human JAr cells in vitro. 2015 Young et al.

(15) Study by Paul Winchester presented at Children's Environmental Network Conference. 4/12/17.

(16) Concerns over use of GBHs and risk associated with exposures – a consensus statement. 2016 Meyers et al.

(17) Cytotoxic and aromatase inhibition by xenobiotic endocrine disruptors alone and in combination. 2007 Benachour el al.

(18) An approach to the identification and regulation of endocrine disrupting pesticides. 2015 Ewence et al.